Short-Term Neonatal Outcome among Term Infants after In-Utero Exposure to Beta Blockers

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ABSTRACT: **Background:** The need for postnatal monitoring of infants exposed to intrauterine beta blockers (BBs) has not been clearly defined.

Objectives: To evaluate infants exposed to intrauterine BBs in order to estimate the need for postnatal monitoring.

Methods: This retrospective case-control study comprised 153 term infants born to mothers who had been treated with BBs during pregnancy. Treatment indications included hypertension 76 mothers (49.7%), cardiac arrhythmias 48 (31.4%), rheumatic heart disease 14 (9.1%), cardiomyopathy 11 (7.2%) and migraine 4 (2.6%). The controls were infants of mothers with hypertension not exposed to BBs who were born at the same gestational age and born closest (before or after) to the matched infant in the study group.

Results: Compared to the control group, the infants in the study group had a higher prevalence of early asymptomatic hypoglycemia (study 30.7% vs. control 18.3%, $P = 0.016$), short symptomatic bradycardia events, other cardiac manifestations ($P = 0.016$), and longer hospitalization ($P < 0.001$). No life-threatening medical conditions were documented. The birth weight was significantly lower for the high-dose subgroup compared to the low-dose subgroup ($P = 0.03$), and the high-dose subgroup had a higher incidence of small-for-gestational-age ($P = 0.02$).

Conclusions: No alarming or life-threatening medical conditions were observed among term infants born to BB treated mothers. These infants can be safely observed for 48 hours after birth close to their mothers in the maternity ward. Glucose follow-up is needed, especially in the first hours of life.

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KEY WORDS: maternal beta blockers (BBs), neonatal hypoglycemia, neonatal outcome, term newborn

Maternal beta blockers (BBs) are used for various clinical conditions during pregnancy, including hypertension, cardiac diseases and arrhythmias, and migraines. Among women with chronic medical conditions, treatment begins before pregnancy and continues throughout. In the case of acute conditions such as pregnancy-induced hypertension or pre-eclamptic toxemia, treatment begins during pregnancy, close to delivery. Use of BB medications during the first trimester is considered safe in terms of the risk for congenital malformations [1,2]. However, these medications have been shown to be related to intrauterine growth restriction (IUGR), preterm deliveries, and perinatal mortality [2-10].

Maternal use of BBs close to delivery has been reported to be related to various neonatal clinical conditions, including hypoglycemia, respiratory distress, neonatal bradycardia, hypotension, patent ductus arteriosus (PDA), and neonatal jaundice [1,5,7,11-13]. The impact of maternal BB use on neonatal outcome has not been fully studied, leading to a lack of appropriate recommendations regarding the management of postnatal follow-up.

Previous reports have led many neonatal departments, including ours, to monitor and observe newborn infants exposed in utero to BBs. This monitoring resulted in depriving them the benefits of mother-and-child rooming-in and had the potential to interfere with breastfeeding as well as to delay parent-child bonding.

In this study our aim was to evaluate short-term neonatal clinical signs among term and late preterm infants exposed in utero to BB medications in order to assess the need for postnatal monitoring and observation and to evaluate associated symptom severity and duration.

PATIENTS AND METHODS

This retrospective study comprised infants born to mothers who were treated with BBs during pregnancy and until delivery and as controls, infants who were born to mothers with hypertension who were not treated with BBs. We reviewed the medical files of term and late preterm newborn infants born at the Sheba Medical Center during a period of almost 5 years (June 2011 to March 2015). According to our department protocol, infants whose mothers were treated with BBs were monitored in a secondary level care unit, a special care infant unit that includes cardiorespiratory monitoring, for 48 hours after birth. The protocol includes capillary blood pre-feeding glucose measurements using a Glucometer Elite XL (Bayer, Tarrytown, New York, USA) taken at hours 1, 2, 4, and 6 of life and every 8 hours thereafter

to complete a 48-hour follow-up. All asymptomatic infants with recorded glucose values in the range of 30–40 mg/dl receive glucose treatment (orally 10% glucose 2 ml/kg). Infants with glucose values lower than 30 mg/dl and those with repeated values in the range of 30–40 mg/dl were treated with continuous intravenous (IV) glucose after an IV bolus of 10% glucose 2 ml/kg. Feeding was initiated (either breast milk or formula) during the first 2 to 4 hours of life and every 2 to 3 hours thereafter or on demand. Breastfeeding is encouraged for all infants.

Excluded from this study were infants born to mothers who, in addition to BBs, used psychiatric medications (such as opiates, benzodiazepines, and tricyclic antidepressants), which may affect postnatal clinical signs, and infants whose mothers consumed alcohol or drugs during pregnancy. Mothers treated with low doses of selective serotonin reuptake inhibitors (SSRI) were included since our previous study had shown a poor correlation between intrauterine SSRI exposure and symptoms, such as hypoglycemia and bradyarrhythmias [14].

The collected maternal data included maternal diseases during pregnancy (hypothyroidism, hypertension, gestational diabetes); group B streptococcus carriers; prolonged rupture of membranes (defined as rupture of membranes > 18 hours before delivery); meconium-stained amniotic fluid; and the type, dose, indications, and duration of BBs used. Treatment was defined as acute if the mother took BBs for 2 weeks or less prior to delivery and as chronic if the mother took BBs for longer than 2 weeks prior to delivery. BB doses were considered to be high when the propranolol dosage was 80 mg/d or higher, the labetalol dosage was 800 mg/d or higher, or the metoprolol dosage was 150 mg/d or higher.

Infant data included gestational age (GA), birth weight (BW), weight for GA (appropriate small-for-gestational-age [SGA ≤ 10th percentile] or large-for-gestational-age [≥ 90th percentile]), gender, Apgar score at 1 and 5 minutes, congenital malformations, postnatal complications (such as respiratory distress, usage and duration of oxygen, or antibiotic treatment), cardiac anomalies (such as PDA, persistent foramen ovale [PFO], or any cardiac malformation documented by an echocardiogram), neonatal hypoglycemia (defined as glucose < 40 mg/dl on the first day of life), and day of hospital discharge.

The controls selected for each infant in the study group were infants who were not exposed to BBs, born to mothers with hypertension during pregnancy at the same GA (completed weeks of gestation), and born closest to the matched infant in the study group. Our department protocol for infants of mothers with hypertension includes capillary blood pre-feeding glucose measurements taken at hours 1, 2, 4, and 6 of life. Data recorded for infants in the control group included the same demographic and clinical data as those in the study group.

The study was approved by the center's institutional research ethics board acting according to the declaration of Helsinki, which also waived the need for patient consent.

STATISTICAL ANALYSIS

Continuous variables were compared using analysis of variance. Categorical variables were compared using Pearson's chi-square test or Fisher's exact test. A P value of < 0.05 was considered significant. Statistical analyses were performed using Statistical Package for the Social Sciences software version 15 (SPSS Inc., Chicago, IL, USA).

RESULTS

During the study period, 157 term and late preterm infants were born in our center to mothers who were treated with BBs during pregnancy. Four mother–infant pairs were excluded due to other psychiatric medications taken by the mothers. The remaining 153 mother–infant pairs comprised the study group.

Medications taken during pregnancy included levothyroxine (11 of the study group and 10 of the control group), calcium channel blockers (11 study and 3 control), SSRIs (6 study and 2 control), and furosemide (8 study).

Table 1 presents the characteristic data of the study group infants and their matched controls. The data indicate that more mothers in the study group had diabetes and delivered by elective (planned) cesarean section compared to controls. The infants in the study group had a higher prevalence of early asymptomatic hypoglycemia, although the need for IV glucose was similar for both groups [Table 2]. Cardiac outcome among the study group infants included PFO in 12 infants, a small

Table 1. The characteristics data for infants of mothers treated with beta blockers and matched controls

Characteristic	BB (n=153)	Control (n=153)	*P* value
Gestational age (week) – median, IQR (range)	38, 37-39 (35–42)	38, 37-39 (35–41)	0.994
Birth weight (gram) mean ± SD	2983 ± 557	3062 ± 438	0.174
Gender Male Female	 76 (49.7%) 77 (50.3%)	 82 (53.6%) 71 (46.4%)	0.647
AGA SGA LGA	120 (78.4%) 24 (15.7%) 9 (5.9%)	135 (88.2%) 13 (8.5%) 5 (3.3%)	0.071
Delivery Partum spontaneous Caesarean section elective Caesarean section urgent Instrumental	 70 (45.8%) 47 (30.7%) 26 (17%) 10 (6.5%)	 101 (66%) 12 (7.8%) 33 (21.6%) 7 (4.6%)	< 0.001
Apgar 1 min < 7	1 (0.7%)	2 (1.3%)	1.000
Apgar 5 min < 7	1 (0.7%)	0 (0%)	1.000
Meconium-stained amniotic fluid	17 (11.1%)	11 (7.2%)	0.322
Maternal age, mean ± SD	34.1 ± 5.6	33.1 ± 5.6	0.133
Maternal diabetes	27 (17.6%)	12 (7.8%)	0.016
Prolong rupture of membranes	6 (3.9%)	12 (7.8%)	0.224
Magnesium treatment	7 (4.6%)	10 (6.5%)	0.619

AGA = appropriate for gestational age, BB = beta-blockers, IQR = interquartile, LGA = large for gestational age, SD = standard deviation, SGA = small for gestational age

Table 2. The neonatal outcomes for infants of mothers treated with beta blockers and matched controls

Outcome	BB (n=153)	Control (n=153)	*P* value
Respiratory distress	4 (2.6%)	5 (3.3%)	1.000
Feeding difficulty	1 (0.7%)	0 (0%)	1.000
Regurgitation	10 (6.5%)	9 (5.9%)	1.000
Cardiac conditions	15 (9.8%)	4 (2.6%)	0.016
Bradycardia	6 (3.9%)	0 (0%)	0.030
Hypoglycemia	47 (30.7%)	28 (18.3%)	0.016
Intravenous treatment of hypoglycemia	18 (11.8%)	16 (10.5%)	0.856
Feeding Breast milk feeding Formula feeding Combined	 32 (20.9%) 42 (27.5%) 79 (51.6%)	 45 (29.4%) 32 (20.9%) 76 (49.7%)	0.165
NICU hospitalization	0 (0%)	4 (2.6%)	0.123
Discharge day - median, IQR (range)	4, 3-5 (2-23)	3, 2-4 (2-11)	< 0.001

BB = beta-blockers, IQR =interquartile, NICU = neonatal intensive care unit

ventricular septal defect in 2 infants, and supraventricular tachycardia in one. Bradycardia of less than 100 beats per minute (BPM) was recorded among six infants in the study group, with the lowest recorded heart rates of 61–91 BPM. Four infants had a single event of bradycardia on the first day of life and two infants had bradycardia on the second day of life. These six infants with documented bradycardia were asymptomatic and they were discharged following 24 hours of non-bradycardic heart monitoring. No infant in the study group needed neonatal intensive unit (NICU) hospitalization. Among the controls, NICU admissions were due to respiratory distress in two infants, and one incident each of a cyanotic event, bradycardia, distended abdomen, and bilious vomiting.

We compared a subgroup of infants who were exposed to high doses of BBs (n=24) to a subgroup of infants who were exposed to low doses of BBs (n=129). Birth weight was significantly lower among the high-dose subgroup than the low-dose subgroup (mean 2758 g vs. 3026 g, respectively, $P = 0.03$). The high-dose subgroup also exhibited a higher incidence of SGA (33% vs. 12.4%, respectively, $P = 0.02$). The main etiology for BB treatment among the high-dose subgroup mothers was cardiac disease (66.7% had arrhythmias, rheumatic heart disease and cardiomyopathy), whereas the main etiology (53.6%) was hypertension among the low-dose subgroup mothers ($P = 0.004$). More mothers in the high-dose subgroup were treated with other medications, such as magnesium, diuretics, and calcium channel blockers, but the difference did not reach a level of significance (33.3% vs.15.5%, respectively, $P = 0.205$). Maternal diabetes was lower among the high-dose subgroup mothers compared to the low-dose subgroup mothers, but that difference also did not reach a level of significance (4.2% vs. 20.2%, respectively, $P = 0.08$).There were no differences in any short-term neonatal complications between these two subgroups.

DISCUSSION

Research has shown that BB treatment during pregnancy has an impact on pregnancy outcome, including premature labor, IUGR, and perinatal mortality [2-8]. The influence of maternal BB treatment on perinatal outcome has not been investigated in depth. To evaluate the impact of maternal BB use, our study included all mothers treated with BBs for hypertension as well as for other indications. We decided to focus on short-term neonatal outcomes to evaluate the need for specific postnatal monitoring and follow-up. We found a high prevalence of early asymptomatic hypoglycemia and a higher incidence of cardiac conditions, which consisted mostly of PFO and mild asymptomatic bradycardia. No life-threatening medical conditions or need for NICU hospitalization were documented among the infants in the study group.

The indication and duration of BB treatments were, as expected, related to maternal medical conditions. Prolonged treatment was associated with chronic pre-pregnancy medical diseases, such as chronic hypertension, cardiac arrhythmias, and migraine. Short treatment (pregnancy duration) was indicated mostly by PIH and pre-eclampsia involving higher rates of magnesium treatment for the hypertension indication, and emergency cesarean section due to severity of maternal hypertension.

Previous studies have shown a correlation between BB use during pregnancy and IUGR/SGA outcome [2-8,10]. In most studies, the rate of SGA newborns with intrauterine BB exposure was compared either to exposure to different antihypertensive medications or to controls comprised of mothers with gestational hypertension, which may also be risk factor for SGA newborns. The rate of SGA among the neonates in the study group in the current study was a bit higher compared to that of the controls and to what is expected in the general population (10%) but it was not statistically significant. Lower birth weight and high SGA prevalence were found only among infants with intrauterine exposure to high doses of BBs. This observation can, however, also be explained by other prenatal maternal medical conditions. Indeed, we found that these subgroups had different maternal characteristics, such as different etiologies for BB treatment, prevalence of diabetes, and a trend of treatment with multiple medications, all of which potentially impact the results. Despite the relatively small sample in the current study, with the exception of lower birth weight, high doses of BBs did not seem to influence neonatal outcome.

Most notable among our results was the high rate (~30%) of early hypoglycemia among the study group. In a large American study, Bateman et al. [12] found a significantly elevated risk (4.3%) of neonatal hypoglycemia after fetal exposure to BB, with an adjusted odds ratio of 1.68 (1.2% in the unexposed group). It should also be noted that in addition to intrauterine BB exposure, there are two other risk factors that may independently contribute to hypoglycemia, maternal diabetes, and SGA, which

were more prevalent in the study group. Hypoglycemia among newborn infants exposed to BBs could be up to 50% [7,11]. Indeed, selective as well as non-selective BBs have been shown to reduce insulin-mediated glucose uptake and possibly inhibit insulin secretion from the β-cell of the pancreas [5]. Despite relative contraindications for the use of BB medications among diabetic patients, almost 18% of the mothers in our cohort were diabetic. Meidah Peterson et al. [3] and Magee et al. [4] have also included women treated with BBs and diabetics. Most of the cases of hypoglycemia, however, appeared early and were asymptomatic and transient following a single dose of oral glucose.

Another concern of neonatal complications among BB-exposed newborn infants is the potential for cardiac involvement, mostly bradyarrhythmias. Bateman et al. [12] reported a significant elevated risk of neonatal bradycardia: 1.6% in the exposed vs. 0.5% in the unexposed, with an adjusted odds ratio of 1.29. Previous studies describing bradycardia events did not provide information about timing, duration, and severity of the events. With the exception of recommendations for postnatal follow-up, there are no clear-cut guidelines for follow-up management. These reports have led many neonatal departments, including ours, to monitor and observe newborn infants that were exposed in utero to BB medications, thereby depriving mother and child of the benefits of rooming-in and delaying parent-child bonding. We found a few cases of mild, self-limited, asymptomatic bradicardia events in the first two days of life with no life threatening medical conditions or need for NICU hospitalization. Cardiac involvements that were more common among the study group mothers included PDA and PFO, as previously described [11]. In accordance with the report by Dubois and coauthors [15], we did not find any other neonatal complications, such as low Apgar score, respiratory distress, feeding difficulties, jaundice and regurgitations. These findings are contradictory to a previous study by Davis and colleagues [1].

LIMITATIONS

This study is retrospective. In addition, the control group included infants of hypertensive mothers who had not been treated with BBs. It can be assumed that hypertension was milder among control mothers, and this may have affected the differences in outcome. Last, the study and control groups were not similar in terms of disease etiology, severity, or other maternal comorbidities, such as diabetes and multiple medical treatments, which may well influence neonatal outcomes, such as birth weight, blood sugars.

CONCLUSIONS

No alarming or life-threatening medical conditions were observed among term infants born to BB-treated mothers. These infants can be safely observed for 48 hours after birth close to their mothers in the maternity ward. Glucose follow-up is needed, especially in the first hours of life.

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"It is impossible to enjoy idling thoroughly unless one has plenty of work to do. There is no fun in doing nothing when you have nothing to do. Wasting time is merely an occupation then, and a most exhausting one. Idleness, like kisses, to be sweet must be stolen"

Jerome K. Jerome (1859–1927), humorist and playwright